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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/580,987	05/25/2006	Zhiwen Zhang	54-001021US	5846

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EXAMINER	
LEAVITT, MARIA GOMEZ	
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1633	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/580,987	ZHANG ET AL.	
	Examiner	Art Unit	
	MARIA LEAVITT	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 May 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/31/07;10/04/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response of 05/30/2008 has been entered. Claims 34-55 a re pending, claims 1- 33 and 56- 61 have been cancelled and claim 34 has been amended by Applicants' amendment filed on 05-30-2008. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election was treated as an election without traverse (MPEP § 818.03(a)).

The requirement is still deemed proper and is therefore made FINAL.

Throughout the instant Office action, the Examiner will use the following abbreviations, which are consistent with Applicants use of said terms: orthogonal aminoacyl-tRNA synthetase, (O-RS), orthogonal tryptophanyl-tRNA synthetase (O-TrpRS), orthogonal mutant tryptophanyl-tRNA synthetase (O-muTrpRS), orthogonal tRNA (O-tRNA) and modified opal suppressor $tRNA^{Trp}$ ($mutRNA^{Trp}_{UCA}$).

Therefore, claims 34-55 are currently under examination to which the following grounds of rejection are applicable.

Information Disclosure Statement

The information disclosure statements filed on October 04, 2006 and December 31, 2007 have been reviewed, and their references have been considered as shown by the Examiner's initials next to each citation on the attached copies.

The information disclosure statement filed on October 04, 2006 and December 31, 2007 fail to comply with 37 C.F.R. § 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or

that portion which caused it to be listed. The following references were not considered for the reasons described below:

References 01, 02, 03 Kowal et al., 03 Ulmasov et al., and 04 of the IDS filed on October 04, 2006 are incomplete in the absence of a legible copy.

References 01 and 02 of the IDS filed on December 31, 2007 are incomplete in the absence of a legible copy.

All other documents in said Information Disclosure statement were considered as noted by the Examiner initials in the copy attached hereto.

Claim objection

Claim 35 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 35 recites, "a tryptophan analog". However, claim 34 has been amended to recite "5-substituted tryptophan". Tryptophan analogs are not necessary all 5-substituted tryptophan analogs as they can be substituted at other positions, e.g., the 7-azatryptophan or Methyl-DL-tryptophan, beta-(3-benzofuranyl)-DL-alanine.

Claim 41, subpart e) is objected to because is unclear what the pVal144ProBsTrpRS stands for. Abbreviations such as pVal144ProBsTrpRS should be spelled out at the first encounter in the claims. Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 41 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 41, subpart c) recites "which hybridizes under stringent conditions over substantially an entire length of a polynucleotide sequence". The term "substantially" is a relative term. It is unclear to what extend the polynucleotide sequence hybridizes to the complementary sequence, 50%, 80% or 100%?. As such, the metes and bounds of the claims cannot be determined.

Claim Rejections - 35 USC § 112 – Scope of enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 34-55 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method of incorporating a 5-substituted tryptophan unnatural amino acid into a peptide, the method comprising,

preparing a construct comprising a nucleic acid sequencing consisting of SEQ ID No. 1 encoding the orthogonal mutant tryptophanyl-tRNA synthetase (O-muTrpRS) of SEQ ID No. 2,

preparing a construct comprising nucleic acid sequencing consisting of SEQ ID No. 3 encoding a orthogonal tRNA (O-tRNA),

introducing into a mammalian cell the O-muTrpRS construct and the O-tRNA construct and preferentially aminoacylating the expressed O-tRNA with the 5-subtituted tryptophan unnatural amino acid, wherein said aminoacylation is catalyzed by the expressed O-muTrpRS,

does not reasonably provide enablement for a genus of unspecified orthogonal aminoacyl-tRNA synthetase fragments and/or variants having at least 90% identity to SEQ ID No. 2 (e.g., the O-muTrpRS polynucleotide sequence of SEQ ID NO: 1 encodes the amino acid sequence of SEQ ID NO: 2), and a genus of undetermined O-tRNA wherein O-RS preferentially aminoacylates a O-tRNA with a 5-substituted tryptophan unnatural amino acid.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the

relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The instant invention is drawn to methods for incorporation of an unnatural 5-hydroxy-L-tryptophan amino acid into a peptide using an orthogonal mutant *Bacillus* tryptophanyl-tRNA synthetase /tRNA pair. The specification teaches one *B. subtillis* orthogonal tryptophanyl-tRNA synthetase (O-muTrpRS)-opal suppressor tRNA ($mutRNA^{Trp}_{UCA}$) pair was generated for use in mammalian cells (p. 59, [0158]). The specification discloses the construction of both, the mutant tryptophanyl-tRNA synthetase (O-muTrpRS) and the mutant suppressor $tRNA^{Trp}$ ($mutRNA^{Trp}_{UCA}$). A series of modifications where made in *B. subtilis* tryptopanyl-tRNA synthetase (BsTrpRS) for expression in 293 T cells (p. 63, [0172]). Specifically, the O-muTrpRS mutant is mutated at position 144, wherein a Val was replaced by a Pro, according to the amino acid sequence of SEQ ID NO: 2 (the Val144ProBsTrpRS amino acid sequence) (p. 23, [0067]). Said mutant suppressed the TGA opal mutation indicating that the generated Val-144→ProBsTrpRS mutant was able to selectively charge the 5-HTPP to the opal suppressor tRNA ($mutRNA^{Trp}_{UCA}$). Moreover, the specification discloses the construction of *Bacillus subtilis* (*B. subtilis*) mutRNA.^{Trp} with a suppressor anticodon UCA, i.e., opal suppressor $tRNA^{Trp}$ ($mutRNA^{Trp}_{UCA}$), encoded by the polynucleotide of SEQ ID NO: 3. Hence, the specification teaches the generation of the *B. subtilis* tryptophanyl-tRNA synthetase (O-TrpRS)/opal suppressor $tRNA^{Trp}$($mutRNA^{Trp}_{UCA}$) pair to uniquely charge 5-HTTP into a mammalian protein in response to the codon TGA (e.g., an orthogonal mutant opal suppressor tRNA, can be charged with a 5-subtituted tryptophan unnatural amino acid with an anticodon complimentary to a UGA termination mRNA selector codon, see Specification (p. 26, [0073]).

The claims can be broadly interpreted as comprising a genus of fragments and/or variants of at least 90% identity to the amino acid sequence of SEQ ID No. 2, with the contemplated functionality of aminoacylating any expressed O-tRNA with a 5-substituted- tryptophan analog. In addition, the O-tRNA can be broadly interpreted as comprising an O-tRNA from any species. In addition, claims 41, subparts b) thorough d) limit the invention to a nucleic acid sequences of any undetermined length hybridizing under highly stringent conditions to the complementary sequence , for example, a nucleic acid sequence comprising the 20-mer of SEQ ID No. 1 that could be used in the O-muTrpRS construct. Furthermore, claim 44 further limits the O-muTrpRS to any fragment and/or variant polynucleotide sequence, including any conservative variation of the polypeptide of SEQ ID No. 2 or fragment complementary to the polynucleotide sequence of SEQ ID No. 1 encoding said polypeptide sequence. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires knowledge of an guidance with regards to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modifications), and detailed knowledge of the ways in which the proteins' structure relates to its function. The same is true of a polynucleotide sequence, as the nucleic acid sequence of the polynucleotide directly correlates with the amino acid sequence of the polypeptide. However in this case this disclosure is limited to the O-muTrpRS polynucleotide sequence of SEQ ID NO: 1 encoding the amino acid sequence of SEQ ID NO: 2 and the polynucleotide of SEQ ID No. 3 encoding the opal suppressor $tRNA^{Trp}$ ($mmRNA^{Trp}_{UCA}$). Thereby, specific issues including the functional limitations of O-mTrpRS /O-tRNA wherein the O-mTrpRS with at least 90% degree of identity to SEQ ID

NO. 2, reading on a genus of functional peptides able of aminoacylating the expressed O-tRNA with a 5-substituted tryptophan unnatural amino acid and whether any O-tRNA other than opal suppressor $tRNA^{Trp}$ ($mutRNA^{Trp}_{UCA}$) can be charged with said 5-substituted tryptophan unnatural amino acid have to be examined and considered for patentability regarding the broadly claimed DNA base sequences

The specification provides sufficient guidance in Example 1 for the corresponding pair O-TrpRS/ O-tRNA from *B. subtillis* that can be used to genetically encode an unnatural amino acid (and not endogenous amino acids) in mammalian cells, because the *B. subtillis* O-tRNA is not recognized by any of the aminoacyl-tRNA synthetases in the mammalian endogenous translation system thus preventing aminoacylation of the O-tRNA with endogenous amino acids. Hence Example 1 confirms the inter-species differences in tRNA recognition elements. In other words, *B. subtillis* O-TrpRS can efficiently charge the total tRNA isolated from *B. subtillis* including a *B. subtillis* tRNA with mutation of the anticodon loop *(i.e., B. subtillis* $tRNA^{Trp}$). Additionally, Example 2 teaches the uniqueness of orthogonal pair *B. subtillis* orthogonal tryptophanyl-tRNA synthetase (O-muTrpRS)-opal suppressor tRNA ($mutRNA^{Trp}_{UCA}$) after transfecting mammalian 293T cells with three individual plasmids, pTrptRNA, pFoldon TGA (e.g., UGA termination mRNA selector codon) and mutant pEF6-TrpRS (i.e.,Val144ProBsTrpRS) and demonstrating that opal suppression (UCA) in mammalian cells is dependent on expression of *B. subtillis* orthogonal tryptophanyl-tRNA synthetase (O-muTrpRS)/opal suppressor tRNA ($mutRNA^{Trp}_{UCA}$) pair. Thus, *B. subtillis* orthogonal tryptophanyl-tRNA synthetase (O-muTrpRS) aminoacylates the corresponding *B. subtillis* opal suppressor tRNA ($mutRNA^{Trp}_{UCA}$) with 5-HTPP for suppression of the TGA68 in the mutant foldon construct.

In other words, the generation of the *B. subtilis* tryptophanyl-tRNA synthetase (O-TrpRS)-opal suppressor $tRNA^{Trp}(mutRNA^{Trp}_{UCA})$ pair uniquely incorporates 5-HTTP (e.g., an unnatural amino acid) into a mammalian protein in response to a UGA termination anticodon and the mRNA selector codon. Thus, the orthogonal *B. subtilis* is pair specific and replacement of one element of the pair such as the *B. subtillis* O-tRNA by other species O-tRNA, e.g., *B. stearothermophilus* t-RNA, would necessitate a different cognate synthetase to enable the claimed functionality. Clearly, apart from the *B. Subtilis* orthogonal tryptophanyl-tRNA synthetase (O-TrpRS)-opal suppressor $tRNA^{Trp}$ ($mutRNA^{Trp}_{UCA}$) pair, the as-filed specification does not teach how to select or use any other conservative variants of SEQ ID NO: 1, SEQ ID NO: 2 and SEQ ID NO: 3, or biologically active portion of the nucleotide sequences of SEQ ID NO: 1, SEQ ID NO: 3 and of the amino acid sequence SEQ ID NO: 2 to able to selectively incorporate 5-HTTP or a 5-substituted tryptophan unnatural amino acid into proteins of mammalian cell. There is no description in the specification, as originally filed, of other mutations of other claimed genus of O-tRNA/O-RS pairs wherein the O-RS uniquely recognizes the O-tRNA and selectively charges it with a 5-substituted tryptophan unnatural amino acid, as embraced by the claim limitations. Hence, there is not indication of a structure-function relationship between a genus of O-RS variants of SEQ ID NO: 1 encoding polypeptides of at least 90% identity to SEQ ID NO: 2 and the claimed genus of species of the O-tRNA other than $tRNA^{Trp}(mutRNA^{Trp}_{UCA})$ for the preferential aminoacylation of the O-tRNA with a 5-substituted tryptophan unnatural amino acid so as to the acylated RNA to insert the 5-substituted tryptophan unnatural amino in response to the unique opal suppressor codon.

Without knowing the structure-function relationship of SEQ ID NO: 1, SEQ ID NO: 2 and SEQ ID NO: 3, the ability to predict the effect of mutations on function is highly unpredictable. The skilled artisan understands that one nucleotide change in a DNA molecule or one amino acid change in the polypeptide encoded by the DNA molecule could result in the loss of its biological activity as demonstrated in the generation of sickle-cell anemia wherein on specific amino acid mutation gave rise to the inherited disease (Biochemistry, John Wiley and Sons, 1990, p. 126-129). Likewise, a single replacement of one amino by another i.e. Trp92, in *Bacillus subtilis* tryptophanyl-tRNA synthetase abrogates its functionality. (Chow et al., *J Biol Chem.* 1992 pages 9146-9; Also see Score results for SEQ ID No. 2. Result1). Moreover, earlier findings of the Ngo et al. (1994 Merz et al., (ed.) Birkhauser, Boston, MA, pp 492-495), evidencing the unpredictability of tertiary structure from amino acid mutations in the primary structure of a sequence, are confirmed by the post filing art of Guo et al., (*PNAS*, 2004, pp. 9205-9210). Guo discloses different amino acid tolerance depending on the tertiary structure of the molecule, in particular β strands are less substitutable than α helices, and surface loops that are not involved in DNA binding are the most substitutable (p. 9205, Abstract). The ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution (e.g., additions) of non-essential residues can often destroy activity or prevent the O-RS variants of at least 90% identity to SEQ ID No. 2 from aminoacylating the expressed O-tRNA with 5-hydroxy-L-tryptophan or any 5-substitue tryptophan analogue. Furthermore, even single-nucleotide polymorphism without affecting the amino acid sequence, e.g., a conservative variation not encoding a different amino acid, can

affect folding of a protein and thus alter its function (Kimchi-Sarfaty et al., 2007, Science, pp. 525-528; p. 527, col. 3, last paragraph). While one of skill in the art can readily envision numerable species of nucleic acid sequences that are at least a given % identity to a reference nucleotide sequence (e.g., SEQ ID No. 1) that encodes a polypeptide of at least a given % identity to a recited reference amino acid sequence (e.g., SEQ ID No. 2), one cannot envision which of these also encode a polypeptide with a specified activity. The fact remains that the actual nucleic acid sequences which encode a protein with a particular activity or the actual amino acid sequences of such a protein cannot be envisioned any better when the possible choices are narrowed from all possible sequences to all possible sequences with an arbitrary structural relationship with a known functional sequence. For example, if one skilled in the art were to make a synthetic nucleotide sequence that encoded a polypeptide with at least 90% identity to the reference amino acid sequence, he would be no more able to say whether it encoded an O-RS than if the nucleotide sequence encoded a polypeptide that was only 10% identical to the reference polypeptide sequence. Nor would he be able to say whether the sequence existed in nature. Hence, the predictability of a quaternary structure from conservative mutations in the primary nucleotide/amino acid sequence requires undue experimentation to determine the number of amino acid substitutions, deletions, and/or insertions able to make a O-TrpRS having at least 90% identity to the amino acid sequence of SEQ ID No. 2 paired with any O-tRNA to be functional or even retain partial activity.

In terms of the structural requirements of the O-mTrpRS nucleic acid molecules, claim 41 subparts a)-d) recites an arbitrary structural relationship between the claimed nucleic acid sequence(s) and the single disclosed species of nucleotide sequence and amino acid sequence,

respectively, based upon hybridization of nucleic acid. Hybridization of two nucleic acids, even under high stringency conditions, requires only that the two nucleic acids share between 25 and 50 nucleotides in common. (Kennell, Progr Nucleic Acid Res. Mol. Biol. 11: 259-301, 1971, at the paragraph bridging pages 260-261). Such a sequence encodes only 8-16 amino acids. Consequently the claims embrace polypeptides that could share as few as 8-16 contiguous amino acids in common out of the 330 amino acids of SEQ ID NO: 2. Conversely, a nucleotide sequence that differs in every wobble base from SEQ ID NO: 1, for example, would encode SEQ ID NO: 2, but would not detectably hybridize to SEQ ID NO: 1 under any conditions. Thus, the recited structural relationship is arbitrary since neither the specification nor the prior art discloses any definitive relationship between protein function and % identity or homology at the nucleotide level; and the specification does not describe a single species of nucleic acid that encodes a functional protein that is not either 100% identical to SEQ ID NO: 1 or that encodes a polypeptide that is not 100% identical to SEQ ID NO: 2.

As the result, given the unpredictability of the art and the lack of working example in the instant specification, particularly when taken with the lack of guidance in the specification, it would have required undue experimentation to practice the instant invention to identify an enormous number of methods as broadly or generically claimed, with a resultant identification of a diversity of DNA sequences of at least 90% identity to the amino acid sequence of SEQ ID No, 2 able of aminoacylating any expressed O-tRNA other than opal suppressor $tRNA^{Trp}$ ($mutRNA^{Trp}_{UCA}$) with a 5-substituted tryptophan unnatural amino acid so as to the acylated RNA to insert the 5-substituted tryptophan unnatural amino in response to the unique opal suppressor codon in a mammal cell system as broadly claimed.

. In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Conclusion

Claims 34-55 are not allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

/Maria Leavitt/

Maria Leavitt, PhD
Examiner, Art Unit 1633